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Study Title: Traumatic Brain Injury (TBI) Studies at Grady Memorial Hospital

Protocol Title: Investigation and Comparison of DETECT, ANAM, and Neuropsychological testing in the detection of mild Traumatic Brain Injury (mTBI)

Principal Investigator:

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14. ABSTRACT

The EDIS(Emergency Department Information System) is one of the first and major components of the Grady Health System's plan to implement an EHR (Electronic Health Record) The implementation of the emergency care patient tracking system will provide the infrastructures necessary for the organization to improve medical care and patient flow in its emergency and trauma service and reduce costs as well as enhance the training experience for clinicians and improve the system's disaster management response processes. The system will also support the organization's on-going efforts to meet National Patient Safety goals.

Grady is located in a populous area. Metro Atlanta ranks No.2 in the nation for total population growth, and this is reflected in the volume of care provided at Grady. Each year, Emory University School of Medicine faculty and house staff working at Grady treats more than one hundred thousand patients annually. In 2005, Grady's Emergency Department treated residents from 133 counties of Georgia's 159 counties and reported the highest number of ER visits of Georgia's 177 hospitals.

Grady is also cornerstone of metro Atlanta's disaster response system and is designated by the Georgia Emergency Management Agency and Metropolitan Response System as the regional disaster coordinating hospital for a 22 county metropolitan region. In this capacity, Grady is responsible for collaborating with the Veteran's Administration and the military services to assist hospitals impacted by a disaster or evacuation. This responsibility includes managing patient transfers and sharing resources, personnel and equipment.

In its role as the regional disaster hospital, the EDIS system will enable Grady ED receiving staff to track patients from the disaster site through patient transfer and disposition. The lack of such a system posed many challenges during Grady's post-Katrina disaster coordination from Dobbins Air Force Base-all information about evacuees, their health status, transfer and ultimate location was manually recorded and is now difficult to retrieve in order to study for future disaster preparedness. The system will also be essential for the patients that Grady will care for as the likely recipient of the largest number of casualties in the event of a local disaster.

In the current environment, the predominant method for tracking patients through the emergency care/trauma center is a manual grease board. The lack of automation can lead to delays in patient care and create barriers to move timely communication among clinicians and along the care continuum during the treatment of a patient's emergent conditions.

Ancillary reports are distributed manually, as well as patient transfers and disposition from the emergency room setting are tracked manually. These manual processes can often lead to increases in costs, medical errors and decreases in patient and provider satisfaction. The EDIS will significantly enhance operations in the emergency care/trauma center, ensuring a public health care systems in the country and operates one of the busiest emergency care/trauma centers in the Southeast. These factors alone make Grady an ideal site for the emergency department patient tracking system project.

We hypothesize that the implementation of a comprehensive emergency department information system is the core ingredient in the development of a robust research infrastructure. Development of a robust infrastructure will facilitate the rapid and accurate assessment of patients and more importantly provide the information and data necessary to improve the treatment of traumatic brain injury and compare treatment and outcomes by injury type.

Specific Aims:

1. Develop and refine goal directed therapy for traumatic brain injury.
2. Evaluate the Novel Screening tool and identifying cognitive impairment for mild traumatic brain injury.
3. Develop a robust research infrastructure
4. Comparison of patients by brain injury type

AIM # 1: The purpose of the retrospective analysis of Goal Directed Therapy for Traumatic Brain Injury is to determine current compliance with widely accepted guidelines for the management of adult, blunt-mechanism traumatic brain injury (TBI) patients and assess the overall mortality of this cohort at Grady Memorial Hospital (GMH).

Objectives:

A. Develop a data extraction tool for monitoring compliance with Goal Directed Therapy (GDT) guidelines for the management of acute TBI in the Emergency Department.
B. Assess past compliance with evidence based management of TBI.

AIM # 2: *Display Enhanced Testing for Concussion and mTBI (DETECT)* and *Automated Neuropsychological Assessment Metrics* (ANAM) are two new tools, which are portable and can test neuropsychological performance/cognitive impairment in real time, such as in the military field.

Our study will compare these two novel methods of neuropsychological testing (NPT) to standard outpatient NPT. The DETECT device utilizes a virtual reality visor to present the patient with visual stimuli in order to test standard cognitive functions. DETECT is an immersive technology that may be used in an otherwise loud or distracting environment. The ANAM device administers a battery of NPT on a computer terminal, which may be carried via a laptop into the trauma bay or military field.

Our research will utilize both of these tests to assess patients during treatment in the Emergency Department at GMH for mild traumatic brain injury (mTBI). Patients will complete testing prior to discharge from the Emergency Department. They will receive additional testing, via the standard neuropsychological methods, within one week of their injury. Patient performance on the three modalities will be compared. The effects of potential confounding variables, such as age, concurrent long-bone injury, and basic demographics will also be assessed. Rapid assessment of TBI has the potential to improve patient disposition and outcome. The TBI research grant will allow us to directly compare these novel methods of NPT to standard techniques, within the environment of the Grady trauma center.

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Introduction

Traumatic Brain Injury (TBI) is a devastating public health problem in the United States (US). There are 1.2 million incident cases of TBI per year in the US. This results in 50,000 deaths per year; approximately 1/3 of all reported trauma related mortality in the US. Heath care costs from TBI are estimated to exceed 50 billion dollars annually [1-4]. In the Iraq/Afghan conflicts, prevalence is even higher, as it is estimated that as many as 20% of combat personnel have suffered TBI while in theatre. Some believe that this is a conservative figure, due to lack of reliable, in the field methods of neuropsychological testing. Grady Health System in Atlanta (GHS) has received a grant from the Department of Defense (DoD) to investigate novel methods of assessing and managing acute TBI. *Display Enhanced Testing for Concussion and mTBI* (DETECT) and *Automated Neuropsychological Assessment Metrics* (ANAM) are two new tools, which are portable and may prove to be useful in assessing cognitive impairment in real time, in the military field. Although, diagnosing mTBI is one of the biggest obstacles to improving our understanding, management of TBI patients is also a prevalent issue. Despite the development of guidelines for managing complications of TBI, numerous clinical trials on TBI have failed, due to the variability in care.

Body

While much attention has been focused on the adverse consequences of severe TBI, repetitive incidents of mild TBI are also of great concern. Despite the designation of these injuries as "mild", even a single concussion can cause significant harm and result in long-term problems with memory, cognition, and even personality. Additionally, if a patient sustains a second TBI before recovering from the first, death can follow as a result of second impact syndrome.

The initial phase of this project was the selection and early impleemntation of the EDIS for the Grady Health System. In the spring of 2009, GHS went through an exhaustive section process of major EHR vendors and ultimately chose the "EPIC" product. The initial phase of the DoD project supported the purchase and implementation of the EDIS component of the EPIC software – this component is called ASAP. After a series of implementation steps, the first phase of the ASAP module (triage, tracking and discharge instructions) was installed on March 17, 2010. The remainder of the ASAP module – which will include full CPOE, MD and RN documentation will be installed and operational on October 31, 2010.

One of the biggest obstacles in improving our understanding of mTBI is managing it. AIM 1: This project is a retrospective review to determine current compliance with widely accepted guidelines for the management of TBI. Assessment of the compliance with evidence based management of TBI will be completed by the review of 200 medical records of pre- GDT implementation in the previous two year span. Outcome measures (systolic BP, O2 saturation, temperature, PaO_2, $PaCO_2$, mean arterial pressure, pH, intracranial pressure, hemoglobin, platelet count, INR, serum sodium, and blood glucose) and clinical management methods are

noted in an excel audit tool. Approximately 150 charts have been reviewed for adherence to goal directed therapy guidelines (see appendix E). Once those chart's have been reviewed, we will compare the same GDT parameters prospectively once the final phase of the ASAP Module has been installed on October 31, 2010.

Another obstacle in improving our understanding of mTBI is diagnosing it. This issue that largely centers on the debate over the lack of a clear clinical definition of what constitutes a "concussion". Clinical signs and symptoms of moderate to severe concussion are variable but typically include: loss of consciousness, amnesia, headache, dizziness, confusion, memory loss, blurred vision, unequal pupils, fatigue, and/or nausea. A current method for diagnosing a concussion or mTBI is neuropsychological testing. Neuropsychological testing has been validated in the literature and is capable of detecting the subtle changes that often result from mTBI. There are many aspects of neuropsychological testing, however, that limit its practically in diagnosing mTBI in the Emergency Department (ED) or a field casualty collection point. Neuropsychological testing requires a quiet room with few distractions. It requires a highly trained person to administer and score the tests, as well as interpret the results. Additionally, a typical battery of neuropsychological tests may take several hours to administer, score and interpret.

In this study, additional tests are used in comparison with that of the standard battery of neuropsychological tests. Display Enhanced Testing for Concussion and mTBI (DETECT) and Automated Neuropsychological Assessment Metrics (ANAM) represents tests that are sustainable in the field and within the Emergency Department at Grady Memorial Hospital. The results of the evaluation of these testing units within the big-city ED will provide insight into the practicality of use as fast and effective screening tools in similar environments. The investigation and comparison of DETECT, ANAM, and Neuropsychological study is a randomized cohort study to assess mTBI within the Grady Memorial Hospital Emergency Care Center. Consenting participants undergo the standard battery of Neuropsychological testing, and will be randomized to additional assessments with either the DETECT or ANAM devices (see appendix B and C). Once IRB approval has been obtained, we will begin the screening and enrollment process (see appendix A).

Key Research Accomplishments

- Selection of EDIS (ASAP) and EHR (Electronic Health Record) Product-EPIC
- Defined ASAP Scope, Scheduling, Analysis, Design (EPIC)
- ASAP Validation Session #1-Scope, Initial System Review of Content (EPIC)
- ASAP Validation Session #2-Initial Research Design and Build (EPIC)
- ASAP Validation Session #3 (EPIC)
- Installation of System Hardware (EPIC)
- Begin Super User Training (EPIC)
- EPIC ASAP went live at Midnight on March 17th (EPIC)
- Completed requirements necessary for Federal Human Protocol Use (EPIC)
- Complete Emory and Grady IRB requirements
- Hired Research Staff

- Content Application Testing
- 60/90 Day Go Live Readiness Review (EPIC)
- Independent Application Review (EPIC)
- Dress Rehearsal Complete (EPIC)
- Content Build Out Complete (EPIC)
- Development complete for medium-priority custom reports
- Development complete for low priority custom reports
- Performed thorough literature review on past and current management strategies for treatment of traumatic brain injury (TBI)
- Have currently reviewed approximately 100 charts for adherence to goal-directed therapy guidelines with a final target number to reach approximately 200 charts. This number is based upon a review with our department's statistician to reach the appropriate power and statistical difference
- Defined need for additional research in management of TBI: Why is there a lack of adherence to proven goal-directed guidelines for management of TBI, and what is the cause for this variability. Specifically, in depth analysis of why there is a lack of adherence to TBI treatment guidelines at a major trauma center emergency department, and the effect this lack of adherence has on patient outcomes
- Set the stage for future project: prospective study on the effect of better online monitoring (ie EPIC(in improving adherence to guidelines and thus patient outcomes

Reportable Outcomes

- Exposed and immersed a current fourth year medical student (MS4) interested in a career in academic emergency medicine to the mechanics of conducting clinical research. Includes grant proposal writing obtaining IRB and institution approval, understanding how to design a good research project, performing literature review, and writing manuscripts, in addition to doing the research.
- Dr. Leon Haley Jr., PI, gave a presentation on the status of the project at the Product Line Review Meeting in March of 2010
- Confidentiality Agreement with David Wright, MD and Zenda Technologies (Inventor and stockholder of DETECT)

Conclusion

EPIC Implementation
The implementation of the EPIC system was phased in with installation on March 17 and October 31, 2010, "Go-Live". As a result of assigned dedicated staff to this project, it has been a success in both internal training of staff and end user delivery.

The EPIC System appears posed to reach the goal of tracking patients from the Emergency Room through patient transfer and disposition. Once EPIC is fully functional in October, 2010, it will incorporate patient tracking and electronic health record. The implementation of the emergency care patient tracking system will provide the infrastructures necessary for the organization to improve medical care and patient experience.

We have identified two effective screening tools, Automated Neuropsychological Assessment Metrics, (ANAM) and Display Enhanced Testing for Concussion and Mild Traumatic Brain Injury, (DETECT). The investigation and comparison of DETECT and ANAM and Neuropsychological study is a randomized cohort study to access mTBI within Grady Memorial Hospital Emergency Care Center. Consenting participants undergo the standard battery of Neuropsychological testing and will be randomized to additional assessments with either the DETECT or ANAM assessment metrics.

Protocol
A protocol was written and approved by the IRB for Retrospective Analysis of Goal Directed Therapy for Traumatic Brain Injury Patients, being conducted by our Y3 Medical Student. We are near completion, and once project has been completed journal article (s) for publication will be released.

We have submitted to the IRB our protocol for their approval of, Novel Methods of Neuropsychological Testing in a Level I Trauma Center: A Comparison of DETECT, ANAM, and Standard Neuropsychological Testing. We anticipate a late October, 2010 approval date.

We have set December 1, 2010 to begin the screening and enrollment process, once IRB approval has been obtained

Staff
We are in the process of finalizing training for our staff to learn how to administer the DETECT and ANAM, screening assessment.

We are currently interviewing for another P/T Research Associate to assist with the clinical research activities to include securing Informed Consents from the patients for the TBI project.

We have increased one of our Sub-Investigators from 10% to 20% effort to assist with writing journal articles, protocols, grants and to assist the Project Director.

Administration
The implementation of the EPIC system will also support the organizations on going efforts to meet National Patient Safety goals.

All DoD Quarterly Reports have been submitted for this grant. We have included an additional copy for your review.

We are in the process of review and collaboration with staff for defining additional research in management of TBI.

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Appendix A
Protocol-Pending Approval

Study Title: *Electronic Patient Tracking and Electronic Health Record at Grady Health System in Support of Military Training and Research*

Protocol Title: Novel Methods of Neuropsychological Testing in a Level I Trauma Center*; A Comparison of DETECT, ANAM, and Standard Neuropsychological Testing*

Principle Investigator:
Leon L. Haley Jr., MD, MHSA, CPE, FACEP

Investigators:
Lisa H. Merck, MD, MPH, Hany Atallah, MD, Daniel Wu, MD, Lovette Kaufman Lindon, PhD, Samuel Chang, B.S., Diandria Barber, B.S.

Protocol Version Number: 3.0

Sponsor: The Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC) DoD Award W81XWH-09-2-0145

Study Location: Grady Memorial Hospital Emergency Care Center (ECC) - 80 Jesse Hill Jr. Dr., Atlanta, GA 30303

Grady Memorial Hospital Assurance #: FWA00004534

Reviewing IRB: Emory University IRB - 1599 Clifton Road, 5th Floor, Atlanta, GA 30322

Emory Assurance #: 00005792

Study Duration: September 2009 – December 2011

Abbreviations Index

1. AE	Adverse Event
2. ANAM	Automated Neuropsychological Assessment Metrics Device
3. ANCOVA	Analysis of Covariance
4. AUROC	Area Under the Receiver Operator Characteristic Curve
5. CFR	Code of Federal Regulations
6. CRF	Case Report Form
7. DETECT	Display Enhanced Testing for Concussion and mTBI
8. FDA	Food and Drug Administration
9. FWA	Federal wide Assurance
10. GCRC	General Clinical Research Center
11. GCS	Glascow Coma Scale
12. GMH	Grady Memorial Hospital
13. GOSE	Glasgow Outcome Scale - Extended
14. HHS	Health and Human Services
15. HIPAA	Health Insurance Portability and Accountability Act
16. ICP	Intracranial Pressure
17. IEC	Independent Ethics Committee
18. IRB	Institutional Review Board
19. LAR	Legally Authorized Representative
20. LOC	Loss of Consciousness
21. mTBI	Mild Traumatic Brain Injury
22. NIH	National Institutes of Health
23. NPT	Neuropsychological Testing
24. NRI	Net Re-Classification Index
25. OHRP	Office for Human Research Protections
26. PI	Principle Investigator
27. SAE	Serious Adverse Event
28. SOP	Standard Operating Procedures
29. SOPT	Subject Ordered Point Test
30. SRT	Selective Reminding Test
31. TBI	Traumatic Brain Injury

1. Protocol Title

Novel Methods of Neuropsychological Testing in a Level I Trauma Center; *A Comparison of DETECT ANAM, and Standard Neuropsychological Testing*

2. Principle Investigator and Study Staff

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3. Abstract

Traumatic Brain Injury (TBI) is a devastating public health problem; 1.2 million incident cases are reported per year in the United States (US). This results in 50,000 deaths/year and accounts for 1/3 of all reported trauma related mortality in the US. In the Iraq/Afghan conflicts, prevalence is even higher. It is estimated that as many as 20% of combat personnel have suffered TBI while in theatre. Some believe that this is a conservative figure, due to lack of reliable, "in the field" methods of neuropsychological testing.

Grady Health Systems in Atlanta (GMS) has received a grant from the Department of Defense (DoD) to investigate novel methods to measure acute TBI. *Display Enhanced Testing for Concussion and mTBI* (DETECT) and *Automated Neuropsychological Assessment Metrics* (ANAM) are two new tools, which are portable and can test neuropsychological performance / cognitive impairment in real time, such as in the military field.

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Our research will utilize both of these tests to assess patients during treatment in the Emergency Department at GMH for mild traumatic brain injury (mTBI). Patients will complete testing prior to discharge from the Emergency Department. They will receive

additional testing, via the standard neuropsychological methods, within one week of their injury. Patient performance on the three modalities will be compared. The effects of potential confounding variables, such as age, concurrent long-bone injury, and basic demographics will also be assessed.

Rapid assessment of TBI has the potential to improve patient disposition and outcome. The TBI research grant will allow us to directly compare these novel methods of NPT to standard techniques, within the environment of the Grady trauma center.

4. Background

Traumatic Brain Injury (TBI) is a devastating public health problem in the United States (US). There are 1.2 million incident cases of TBI per year in the US. This results in 50,000 deaths per year and accounts for approximately 1/3 of all reported trauma related mortality in the US. Heath care costs from TBI are estimated to exceed 50 billion dollars annually [1-4]. In the Iraq/Afghan conflicts, prevalence is even higher, as it is estimated that as many as 20% of combat personnel have suffered TBI while in theatre. Some believe that this is a conservative figure, due to lack of reliable, "in the field" methods of neuropsychological testing. Grady Health Systems in Atlanta (GMS) has received a grant from the Department of Defense DoD to investigate novel methods of assessing acute TBI. *Display Enhanced Testing for Concussion and mTBI* (DETECT) and *Automated Neuropsychological Assessment Metrics* (ANAM) are two new tools, which are portable and may prove to be useful in assessing cognitive impairment in real time, such as in the military field.

The CDC estimates that 5.3 million civilian Americans are living with disability from TBI. Survivors of severe TBI (sTBI) typically require 5 to 10 years of intensive rehabilitation

therapy. The lifetime cost of care for a survivor of sTBI can exceed $4 million dollars [5]. TBI is a disease associated with significant morbidity and mortality, and greatly effects civilian and military health in the US.

The devastating consequences of sTBI are immediately apparent. However, mild traumatic brain injury (mTBI) can also lead to disabling concerns. Cognitive deficits including: decreased memory function, impaired reaction time, and damage to higher cortical functions may be difficult to diagnose. However, such injuries often impair an individual's ability to safely perform their job – on the football field, in field combat, or on the highway. Despite the designation of these injuries as "mild", even a single concussion can cause significant harm and result in long-term problems with memory, cognition, and personality. Additionally, multiple fatalities have been reported as "second impact syndrome" when a patient sustains a second TBI before recovering from the first, death can result.

The diagnosis of mTBI or cerebral concussion is complex. Clinical signs and symptoms of moderate to severe concussion include: loss of consciousness, amnesia, headache, visual changes, emesis, weakness, numbness, dizziness, confusion, memory loss, fatigue, and/or nausea. Neuropsychological testing (NPT) has been traditionally used to identify and quantify mTBI. However NPT requires a highly trained individual to administer the examinations. This test takes greater than one hour of time, and a quiet working environment without distractions. A standard battery of neuropsychological tests may take several hours to administer, score and interpret. Such testing has not been implimented in trauma units or in the military theater due to such practical constraints and limitations. NPT has been validated in the scientific literature and utilized clinically to detect the subtle changes that result from mTBI.

Our study will compare two novel methods of neuropsychological testing to standard outpatient NPT. These tools, DETECT and ANAM, utilize portable techniques that can be implemented in the often chaotic, loud, and complicated environments like the trauma bay or military field. The DETECT device utilizes a virtual reality visor to present the patient with images and stimuli that test standard neuropsychological functions. This device is an immersive technology that may be used in an otherwise loud or distracting environment. The ANAM device administers a battery of NPT on a computer terminal, which may be carried via a laptop into the trauma bay or military field. Neither modality requires significant training for the staff who administers the test. Our research will utilize both of these tests to assess patients in the Emergency Department at GMH. Results will be compared between tests and to standard outpatient NPT for each patient within one week of injury.

5. Objectives/Specific Aims/Research Questions

A. Primary Aims

1. Directly compare patient performance after mTBI in the Emergency Department of Grady Memorial Hospital utilizing DETECT and ANAM.

2. Compare patient performance on DETECT and ANAM to standard neuropsychological testing, which is performed within one week after injury at the General Clinical Research Center (GCRC).

B. Secondary Aims

Assess variables that may influence or confound a patient's performance on NPT, these include:

1. Clinical variables- such as concurrent orthopaedic injury, opiod administration, intoxication, and time to testing

2. Demographic variables- such as age, race, sex, and educational status.

6. Study Design and Methods

A. Study Type

This is a cohort study to assess mTBI after admission to the Grady Memorial Hospital Emergency Care Center (GMH ECC) for trauma. Patients identified via the EPIC triage system as presenting with medical complaint of mTBI in the GMH ECC will be approached for participation in the study. After informed consent and review of all inclusion / exclusion criteria, enrolled patients will complete ANAM and DETECT neuropsychological testing in the ED. The order of testing will be randomized between subjects in order to minimize practice effects. Enrolled patients will then return to GMH in order to complete standard NPT within one week of discharge, testing will be completed at the General Clinical Research Center (GCRC).

B. Study Setting

Grady Memorial Hospital (GMH) is one of the busiest Level I Trauma Centers in the Southeastern United States. The ED staff treats more than 100,000 emergencies per year. Greater than 4,000 patients treated at GMH are classified as having a “major” traumatic event via the Trauma Registry of the American College of Surgeons (TRACS) database. Grady is the only Level 1 Trauma Center within a 90-mile radius of downtown Atlanta. Because of its large encatchment area, diverse patient population, and high level of patient acuity, Grady is the training site for Ranger Medics and other non-civilian health care professionals.

C. Study Sample

The study sample will be recruited from 12/1/2010- 12/31/2011. The enrollment goal is to recruit two-hundred mTBI patients. A convenience sample will be utilized to enroll all eligible patients presenting to GMH during study times between 10AM and 10PM. Nurses, physicians, and other medical staff will rapidly identify all patients presenting to the ED with a chief complaint related to TBI. These staff with then page the research associate who will determine eligibility for enrollment. Research personnel will also scan the Emergency Care Center EPIC Tracking Board during study enrollment times – patients may be listed on the tracking board with multiple injuries related to mTBI. The electronic medical record system serves to stratify patients with TBI into readily identifiable groups. Once identified, the patients will be further screened by the research associate. Patients who are eligible for participation will then be presented with the informed consent (see appendix A). Inclusion and exclusion criteria are listed in **Section 6. Patient selection.**

D. Neuropsychological Testing

In the ED the enrolled patient will complete ANAM and DETECT testing. The testing modalities are described below.

1. Display Enhanced Testing for Concussion and Mild Traumatic Brain Injury (DETECT)

The DETECT system is a novel way to implement neuropsychological testing. It has been utilized in the assessment of Dementia, as well as in assessing CHI in football players on the field during games. DETECT presents patients with visual and auditory cues and measures individual response to test stimuli. Rather than

sitting at a desk or computer terminal, the patient is presented with test items while wearing a virtual reality enhanced visor over their head. The visor projects visual images to the subject on a display incorporated into the wrap around visor. The visor is connected to ear phones with noise cancellation technology, so that the patient will be minimally disturbed by surrounding sounds. The patient is given a hand held platform with buttons that to press which record their answers to the NPT. The visor creates an immersive environment for testing. DETECT testing takes approximately 10 minutes to complete.

Due to the device placement on the head, there is a risk of patient discomfort and claustrophobia. The research associate will monitor the patient at all times for discomfort, and patients will be counseled prior to initiating the study, that they may stop testing at anytime should they become uncomfortable. Once activated, DETECT performs a neuropsychological exam in 7-10 minutes. This includes: simple and complex choice reaction time, selective reminding, and subject-ordered pointing. The DETECT system employs 4 tests including: a modified Selective Reminding Test (SRT), complex choice, n-back working memory test, and a modified Subject Ordered Point Test (SOPT).

2. Automated Neuropsychological Assessment Metrics (ANAM)

ANAM is a computer-based desk-top program that takes 20 minutes to complete. ANAM is a compilation of NPT translated into the computer platform to collect data on attention, memory, reaction time and higher cortical abilities. These data are currently used by the US military to help monitor recovery from TBI by comparing patient scores over time.

3. Standard Neuropsychological Testing

The first portion of the study is completed in the ED, the subjects will be then given detailed return instructions and an appointment for follow-up neuropsychological testing at the GCRC within one week. In order to assist in the patient's return to GMH, they will be given a Marta token as compensation for travel related expenses related to their return to outpatient testing.

Standard neuropsychological testing will be administered by a trained neuropsychology research associate in the GCRC within one week of initial injury. Neuropsychological testing consists of seven individual assessments of cognitive function. The NPT chosen is specific to mTBI. The tests will be administered in a quiet environment, over the course of one hour. Upon completion of the outpatient one hour neuropsychological testing, they will also receive 50 dollars in compensation, for the time to complete the assessment. NPT are listed in Table 1.

Table 1. Neuropsychological Battery of Testing Procedures

Test	Measures	Time (minutes)
Paced Serial Addition Task (PASAT)	Information processing speed and working memory	10
Controlled Oral Word Association Test (COWA)	Word list generation	5
Trail Making	Set shifting under timed conditions	10
Selective Reminding Test (SRT)	Word list learning and immediate/delayed recall	10
Wisconsin Card Sorting Test	Hypothesis generation and response shifting	10
N-back Working Memory Task	Working memory with increased load	5
Simple and Complex Choice	Information processing speed	5

Reaction Time

E. Laboratory Evaluations

Patients who have been exposed to alcohol or drugs and who are clinically intoxicated (as quantified by physician judgment, lab data, or breathalyzer test with ETOH level ≥.08) will be excluded from the study. No patient will undergo additional serum testing as part of inclusion in the study. All patients will undergo breathalyzer testing, patients testing as above the legal limit for alcohol intoxication (≥.08) will be excluded from the study. All data concerning lab results will be protected by HIPAA and will also be placed within the confidential research documents. Breathalyzer data and data from neuropsychological testing will not be placed in the medical record.

F. Data Management

Triage nurses in the ED will be responsible for collecting core data elements from patients suspected of having mTBI. These data include: name, sex, age, race, education level, history of dementia or cognitive impairment, signs and symptoms of TBI: loss of consciousness, seizures, nausea/vomiting, headache, dizziness, visual changes, numbness, weakness, GCS score, vital signs, other concurrent traumatic injuries, mechanism of injury, and time of injury. Data on general ED assessment and treatment, such as medication administration will also be collected, via the electronic medical record system, EPIC.

The study will be conducted using electronic data acquisition. Each patient will be assigned a unique identifier upon inclusion in the study. A main lexicon of patient names and unique identifiers will be stored in a locked facility within the Emergency Neurosciences suite. Clinical data will be entered into an Access database by the study staff. Data collection Case Report Forms (CRF) will be developed for entry into the main database. The privacy of study

participants is important to the Grady Memorial Hospital ED. In protecting the health information that identifies our participants, we will follow all requirements of the Health Insurance Portability and Accountability Act (HIPAA). All identifying information will be removed from the case report form and the patients will be identified by unique identifier. Study investigators will all have completed CITI certification.

G. Informed Consent Process

Once a patient has been identified as eligible for the study, they will be approached for Informed Consent (see Appendix A). Consent will be obtained directly from the patients/subject. Neuropsychological testing will only be initiated after all standard medical care is complete and the patient is deemed appropriate for discharge from the ED. Patients will be counseled that their participation in the study is voluntary and that they will receive the standard of care for mTBI even should they refuse to participate in the study.

1. Description of Potential Risks

The DETECT test involves the patient being placed in a visor/ear phone device which may cause emotional discomfort for patients with claustrophobia. This procedure involves minimal risk to patients. Patients will be counseled about the method of DETECT testing as a part of the Informed Consent process, and will additionally be counseled that should they find the process uncomfortable they may stop at any time.

Additional Risks: neuropsychological testing is considered noninvasive. The ANAM , DETECT, and NPT will add approximately 2 hour to the patient's care at GMH. Patients will understand that should they wish not to proceed at any point in care that they may withdraw from the study.

2. Description of Potential Benefits

All participants will not directly benefit from being in this study. However, this research may result in increased speed and accuracy of diagnosis/treatment of mTBI, this is an indirect benefit of study participation.

Additionally, should the neuropsychologist who reviews the patient's study results conclude that they would benefit from outpatient neuropsychological treatment in the TBI clinic at Emory, the patient will receive a referral to this center. All study results will remain confidential.

7. Participant Selection

Inclusion Criteria: Patients will be eligible to participate in the study if they are 18 years of age or older and present to the GMH ED with history of consistent of mTBI due to blunt trauma. Patients with a Glasgow Coma Scale (GCS) of 13-15, history of loss of consciousness (LOC) lasting less than 20 minutes, pre/post traumatic amnesia, or any transient or mildly altered mental state related to the trauma will be included. Patients must be eligible for discharge from the ECC upon inclusion in the study. All examinations will be initiated within 6 hours of injury.

Exclusion Criteria: Age < 18 years, cervical spine trauma, eye injury, polytrauma precluding same day discharge from the ED, GCS <13, prisoner/incarcerated patient, and intoxication (quantified by breathalyzer >0.08 etoh, and/or clinical judgment). Detailed inclusion and exclusion criteria are listed in Table 2.

Table 2. Participant Study Inclusion and Exclusion Criteria

Inclusion Criteria	**Measure**
Blunt Head Trauma	History
Mild Traumatic Brain Injury	History of Trauma GCS (13-15) Amnesia, AMS, or other neurological complaint
Presentation within 6 hours of injury	History
Age ≥ 18	History
Exclusion Criteria	
Intoxicated	Breathalyzer test ETOH > .08, clinical assessment
Unable to wear study device, dominant hand injury, ocular injury	Study personnel assessment
Polytrauma precluding same day discharge	Study personnel assessment
Baseline dementia	Study personnel assessment
Baseline cogniive impairment	Study personnel assessment
Nonenglish speaker	Study personnel assessment
Prisoner or incarcerated patient	History

8. Data Analysis

This observational study seeks to determine whether two competing diagnostic tests (DETECT and ANAM), which are designed to determine the degree of neuropsychological impairment, are non-inferior to a gold standard test, formal neuropsychological testing (NPT). The term "non-inferiority" refers to whether the experimental diagnostic tests (DETECT and ANAM) provide enough accuracy to be considered on par with the gold standard test – even if its accuracy is slightly lower. The perceived advantages of DETECT and ANAM – better mobility, less expensive, greater field utility, less staff training, etc. – might warrant a small trade-off

(determined qualitatively) in accuracy. The aim of the study is to enroll 200 participants. Statistical analyses will be completed by Patrick D. Kilgo, a faculty member in the department of Biostatistics and Bioinformatics at the Emory University Rollins School of Public Health who has experience with DETECT and NPT studies.

A. Statistical Analysis of Primary Aim #1:

The primary aim of the study is compare patient performance after mTBI utilizing DETECT, ANAM, and NPT and to see how well the DETECT and ANAM correlate with NPT. To this end, NPT outcomes, because they are well-validated, will serve as the gold standard for accuracy purposes.

1. NPT Outcomes:

The NPT battery consists of 7 subtests designed to measure different aspects of cognitive function. Each patient will receive a numerical score on each of the seven subtests and each score will represent one outcome. A "global" score that summarizes impairment across the seven tests will be formulated so that a gold standard overall impairment measure can be correlated with DETECT and ANAM items. Further, a qualified neuropsychologist will also review each case and make an ordinal determination of cognitive ability on a four-point scale – No impairment, Possible Impairment, Probable Impairment or Definite Impairment.

2. DETECT Summary Measures

The current DETECT profile consists of five subtests, of which three of them are similar in purpose. Within each subtest, up to 3 "rounds" are administered where the same type of test is given using different props or cues. Data from the rounds within subtests represent the most specific unit of measure being captured. The

structure of the test in each round consists of patients responding to screenshots in the immersive environment by either clicking the 'Yes' or 'No' button. Thus, within each round, repeated responses are recorded for each patient. Summary measures will be calculated pertaining to both accuracy and response time for each patient.

There are four outcomes possible with every mouse click in any round of a subtest.

		Proper Response	
Actual Response		**Yes**	**No**
	Clicked Yes	True Positive (TP)	False Positive (FP)
	Clicked No	False Negative (FN)	True Negative (TN)

If a response results in a TP or TN then the patient has accurately chosent the correct response. In each round of each subtest, the accuracy percentage is tallied as a summary measure for the algorithm consideration. Also, an accuracy measure for the entire subtest (across all rounds) is calculated. Thus, each DETECT subtest has as many as four accuracy summary measures associated with it.

The time (in seconds) from the onset of each flash to the subject's click response is measured. If after three seconds the subject has not responded, the test "times out", the time is recorded as three seconds, and he is moved onto another flash

sequence. A total of two time summary measurements are calculated for each round of each subtest. The first relates to the average response time in a round and the second summary measure is the number of timed-out responses in each round.

3. ANAM Summary Measures

ANAM also delivers measurements of several neuro-cognitive domains. ANAM tests include:

a. Sleepiness Scale – a measure of the fatigue domain.

b. Mood Scale – a measure of the mood domain.

c. Simple Reaction Time– a measure of the reaction time domain. This test is repeated twice to estimate learning effects.

d. Code Substiution (Learning) – a measure of the learning domain.

e. Procedural Reaction Time – a measure of the processing speed domain.

f. Mathematical Processing – a measure of the working memory domain.

g. Matching to Sample – a measure of the spatial memory domain.

h. Code Substitution (Delayed) – a measure of the delayed memory domain.

Each of these tests is scored numerically. Additionally, an ordinal classification variable is provided that indicates whether the patient's performance on each test is similar to similarly-aged controls. This is delineated in three levels – Average or Above, Below Average, and Clearly Below average. Both the numerical and the ordinal scores for each test will

serve as predictors in this study and will be used to build predictive regression models (see below):

4. Statistical Analysis

The NPT outcomes are measured on a continuous scale, as are DETECT and ANAM items. Also, DETECT and ANAM both test for cognitive function in multiple domains, meaning that there are several variables for DETECT and ANAM that will be available for analysis. To this end, general linear regression modeling will be used to model the association between sets of DETECT and ANAM predictors (separately) and the numerical outcomes from NPT. Measures of association including the coefficient of variation (R^2) and univariate Pearson's correlation statistics will be computed. Model selection procedures will be evaluated to determine the best fitting algorithm.

The association between psychologist-determined impairment class (No impairment, Possible Impairment, Probable Impairment or Definite Impairment) and DETECT/ANAM variables will be assessed using an ordinal logistic regression model. The formulation of models will be performed using model selection techniques including the net re-classification index (NRI).

The success of the logistic regression, either in the univariate or multivariable setting, will be evaluated by assessment of the classification table, showing correct and incorrect classifications of impairment class. This includes measures of sensitivity and specificity, positive predictive value, negative predictive value and likelihood ratios associated with each predicted probability threshold. Further, the area under the receiver operator

characteristic curve (AUROC) will be compared using paired tests described by Hanley and McNeil to determine whether DETECT and ANAM models have similar discrimination (the ability to separate cases into the correct impairment classes). The AUROC combines sensitivity and specificity in such a way as to give a robust estimate of the discrimination of the DETECT test.

B. Assessment of Potential Confounders:

Potential confounders including concurrent orthopaedic injury, opiod administration, intoxication, time to testing, age, race, sex, and educational status will be adjusted for in the linear and logistic statistical models and their effect (if any) quantified. Adjusted means, via analysis of covariance (ANCOVA) techniques, will be computed to estimate the raw effect of the DETECT/ANAM predictors.

Descriptive statistics will be used to characterize demographics of the patients enrolled. All tests will be evaluated at the 5% significance level. Missing data will be unlikely due to the prospective nature of the study but instances of omission will be addressed with multiple imputation methods.

This observational study seeks to determine whether two competing diagnostic tests (DETECT and ANAM), which are designed to determine the degree of neuropsychological impairment, are non-inferior to a gold standard test, formal neuropsychological testing (NPT). The term “non-inferiority” refers to whether the experimental diagnostic tests (DETECT and ANAM) provide enough accuracy to be considered on par with the gold standard test – even if its accuracy is slightly lower. The perceived advantages of DETECT and ANAM – better mobility, less expensive, greater field utility, less staff training, etc. – might warrant a small trade-off (determined

qualitatively) in accuracy. The aim of the study is to enroll 200 participants. Statistical analyses will be completed by Patrick D. Kilgo, a faculty member in the department of Biostatistics and Bioinformatics at the Emory University Rollins School of Public Health who has experience with DETECT and NPT studies.

10. Adverse Event Reporting / DSMP:

In order to minimize the risks associated with this study, research staff will be present during the conduction of all testing procedures. The study staff will have specialized training in each of the testing procedures and will be able to assist any patient with questions or concerns. A patient may choose to withdraw from the study at any time.

A. Significant Adverse Event (SAE) Reporting

It is unlikely that our patient population will be vulnerable to SAE given the minimally invasive nature of our study procedures, in this population of patients who have been cleared for outpatient management from the GMH ED.

SAEs are defined according to Emory IRB protocol as: an adverse event occurring at any intervention level that can result but are not limited to any of the following outcomes: death; threat to life; extended hospitalization; disability or incapacity; congenital anomaly or birth defect; cancer; any medical event which requires treatment to prevent one of the medical outcomes listed above.

All AEs will be reported to the Emory University IRB no later than two (2) business days following the event.

1. Roles and Responsibilities of Medical Monitor

N/A

2. Withdrawal from the Protocol

All participants in this research study retain the right to withdraw from the study at any time.

3. Modifications to the Protocol

Modifications to the protocol will be documented as necessary and submitted to Emory IRB and the DoD for approval.

4. Protocol Deviations

Protocol deviations are defined as any unanticipated situation during the testing procedures that adversely affects any of the following:

1. The rights, welfare or safety of the subjects
2. The integrity of the research study data
3. The subjects willingness to continue participation in the study
4. the health of the subjects

Protocol Deviations will be reported to the Emory University IRB via the Protocol Deviation form.

12. Study Personnel

A. Principal Investigator Roles and Responsibilities

The PI will supervise and oversee the research process, budget, and will be responsible for the investigators and staff at GMH. The PI will ensure compliance with all research protocols and IRB. The PI will protect the safety and welfare of research participants; ensure compliance with the protocol's data and safety monitoring plan, and report adverse events to the Emory IRB and the DoD.

B. Study Staff Roles and Responsibilities

The study staff will perform any and all research related procedures in accordance with study protocol. They will obtain informed consent from all research subjects. The staff

will have completed CITI and HIPAA training. The study staff will comply with all procedures within the protocol and report adverse events to the PI.

C. Conflict of Interest

Study staff will report any conflicts of interest to the PI and IRB.

Appendix A

Grady Healthcare
Consent to be a Research Subject

Title: *Novel Methods of Neuropsychological Testing in a Level I Trauma Center;* A Comparison of DETECT ANAM, and Standard Neuropsychological Testing

Principal Investigator: Dr. Leon L. Haley Jr., MD, MHSA, CPE, FACEP

Sponsor: The Department of Defense (DOD) Telemedicine and Advanced Technology Research Center (TATRC)

Introduction

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

Before making your decision:

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear
- Feel free to take home an unsigned copy of this form and take your time to think about it and talk it over with family or friends

You can take a copy of this consent form and the date, to keep. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. By signing this form you will not give up any legal rights.

Study Overview

Traumatic Brain Injury (TBI) is a large public health problem. There are 1.2 million cases of TBI per year in the United States (US). This results in 50,000 deaths/year and accounts for 30% of all reported traumatic deaths in the US. In the Iraq/Afghan war, TBI has effected thousands of soldiers.

Researchers believe that even more people may have TBI, but it is difficult to measure brain injury "in the field" such as while at war, and so cases may go undiagnosed. Testing for TBI, or "neuropsychological testing" (NPT) has previously been completed by medical specialists

and has required quiet testing facilities. Grady Health Systems in Atlanta (GMS) has received a grant from the Department of Defense (DoD) to study two new ways to measure TBI.

These new tests are called "*Display Enhanced Testing for Concussion and mTBI* "(DETECT) and "*Automated Neuropsychological Assessment Metrics"* (ANAM). These new tools are portable and may be able to test brain injury even in loud or complex places such as in the Emergency Department or military field.

You have been asked to be a part of this study because your doctors have diagnosed you with a minor TBI or minor brain injury. The testing in the study will compare the two new methods to the tests that are in practice now.

Your participation in this study is voluntary and you can stop at any time, even if you have already started testing. If you refuse testing, you will still receive the standard care for TBI in the Emergency Department.

Should you choose to be a part of the study, you will also receive the additional testing, DETECT and ANAM, which may further identify an injury that can be treated. If such an injury is identified, then you will be referred to a specialist, should you wish to receive additional care.

Testing will not interfere with your medical treatment in the ED. The records from your testing, as a part of this research, will not be a part of your medical record. They will be stored in a separate research file that is confidential.

Fast diagnosis in TBI may improve patient outcomes. This study is important as it will allow us to compare new tests for TBI to the standard tests, within the busy environment of the Grady trauma center.

Procedures

Brain injury is sometimes measured with a special type of testing that evaluates thought processes, such as how quickly you answer questions and how you remember words or pictures. This is called "neuropsychological testing" (NPT). NPT can detect small changes in thinking that result from brain injury.

The purpose of this study is to compare three ways to complete NPT. The traditional way to test brain injury is to have a highly trained interviewer ask questions in a quiet room. This takes about one hour. This type of NPT is not usually done in the Emergency Department (ED), because it is not practical. The ED can be noisy and patients do not usually stay extra time for specialized NPT testing. Patients with TBI are often given appointments to have this test in an outpatient clinic, after they are discharged from the ED.

If you agree to participate in this study, you will take two new kinds of NPT in the Emergency Department. These types of NPT are faster than the standard NPT testing. They take between ten and twenty minutes to complete. These tests use computers. They are described in more detail below. The order in which you take the tests will be chosen randomly by a computer. This means that there is a 50/50 chance that you will take test #1 first, and a 50/50 chance that you will take test #2 first.

1. Display Enhanced Testing for Concussion and Mild Traumatic Brain Injury (DETECT)

DETECT is a new way to test brain function. In order to use DETECT, you wear a visor, (like a pair of goggles) over your eyes and headphones over your ears. A research associate will help you put this visor on. The goggles show pictures through the visor while the headphones present sounds and keep out background noise. Once turned on, DETECT will present you with questions to test brain function such as reaction time and memory. DETECT takes 7-10 minutes to complete the NPT. If at anytime you wish to stop testing or are uncomfortable in any way, you can tell the researcher who will stop the test. You will continue to receive standard care in the Emergency Department whether or not you complete this test.

2. Automated Neuropsychological Assessment Metrics (ANAM)

ANAM is a computer program that also presents NPT. In order to take ANAM you will sit with a computer and our research associate will help you start the program. You will answer questions on the computer by pointing and clicking with the hand held mouse. ANAM measures your ability to react, remember items, and think through problems. This test should take about twenty minutes to complete.

If at anytime you wish to stop testing or are uncomfortable in any way, you can tell the researcher who will stop the test. You will continue to receive standard care in the Emergency Department whether or not you participate in the research.

3. Standard Neuropsychological Testing (NPT)

If you choose to be a part of this research study, you will be asked to return to Grady within one week for a follow-up visit. Standard NPT will be done at the General Clinical Research Center (GCRC) at Grady Memorial Hospital.

You will be given an appointment for this test before you leave the ED. Our research team will provide you with a MARTA token for transportation costs back to Grady.

A research associate will sit with you in a quiet room at the GCRC and ask you questions. The questions measure your ability to react, remember items, and think through problems. The NPT takes about one hour to complete. If at anytime you wish to stop testing or are uncomfortable in any way, you can tell the researcher who will stop testing.

After completion of the NPT at the GCRC you will be provided with fifty dollars in compensation for the time that you spent on the research project.

Summary of NPT: NPT is not regulated by the Food and Drug Administration (FDA). These tools are one part of an assessment for TBI. More information is needed in order to make a diagnosis or treatment plan for TBI.

The results of your NPT will be reviewed by a specialist. If this doctor thinks that you would benefit from further medical care, we will provide you with a referral for care with a brain specialist.

4. Additional Procedures

There are no blood draws or x-rays as a part of this research.

Your medical history and records from the ED will be reviewed. All health records will be kept confidential.
If you are 18 years of age or older and diagnosed with a mild traumatic brain injury mTBI you are eligible to be screened for the study. If you agree to be in the study, our researchers will make certain that you are eligible to be included in the study.

If as part of the treatment of your injury you are going to be admitted to the hospital, or if you have received a lot of pain medications- you may not be able to complete testing and you will not be enrolled in this study.

If your condition worsens, or if you have serious injuries identified during your care you will not be enrolled in the study.

All participants in the study will complete a breathalyzer screen for alcohol use. The breathalyzer is a machine that you will blow air into from your mouth. It measures the presence of alcohol. Alcohol can effect thinking. If your breathalyzer screen is equal to >0.08 then you will not be enrolled in the study.

The screening described above is confidential to your research file, and will not be a part of your GMH ED record.

Risks and Discomforts

It is unlikely, but there may be side effects from the procedures that are not known at this time. Additionally, your condition may not get better as a result of your being in this study.

The most common risk or discomfort expected in this study is:
Mild awkwardness of testing, such as discomfort in having the DETECT visor over your eyes, this is sometimes called claustrophobia. If you are uncomfortable with the DETECT visor, or with working on a computer in the ED, the research associate will help you stop testing at any time. Testing does take extra time and will prolong your stay in the ED. You may decide that

you do not wish to complete testing in the ED or in the clinic. Should you wish to stop at any time, notify the research associate.

There is a risk that you will be counseled that you may benefit from further care for TBI. This information may be concerning. If an injury is identified, our research team will refer you to social work and to specialists in brain injury.

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Benefits

This study is not designed to benefit you directly. Your traumatic brain injury may improve while you are in this study but it may not, and it may even get worse. This study is designed to learn more about traumatic brain injury. The study results may be used to help others in the future.

Compensation

You will receive a MARTA token after completion of the ED portion of your visit.
After you complete the GCRC study visit you will receive $50.00.
You will receive $50.00 total, if you complete all study visits.

Other Treatment Outside this Study

If you decide not to enter this study, there is care available to you outside of this research. You can be referred to a brain injury physician for further evaluation in clinic. The research associate will discuss this with you. You do not have to be in this study to be treated for minor traumatic brain injury.

Confidentiality

Certain offices and people other than the researchers may look at your medical charts and study records. Government agencies and Emory or Grady Healthcare employees overseeing proper study conduct may look at your study records. These offices include the Office for Human Research Protections, the Department of Defense, the Emory or Grady Healthcare Institutional Review Board, the Emory or Grady Healthcare Office of Research Compliance and the Office for Clinical Research. Study sponsors may also look at your study records. Emory or Grady Healthcare will keep any research records we create private to the extent we are required to do so by law. A study number rather than your name will be used on study records wherever possible. Your name and other facts that might point to you will not appear when we present this study or publish its results.

Study records can be opened by court order. They may also be produced in response to a subpoena or a request for production of documents.

Research Information Will Not Go into the Medical Record

If you are or have been an Emory or Grady Healthcare patient, you have an Emory or Grady Healthcare medical record. If you are not and have never been an Emory or Children's

Healthcare patient you do not have one. Please note that an Emory or Children's Healthcare medical record will **not** be created for you just because you are in this study.

To better protect the confidential nature of your research information, the results from these study tests and procedures should **not** be included in any medical record you have:
Neuropsychological testing completed in the ED via DETECT or ANAM.
Neuropsychological testing completed in the GCRC as part of this study protocol on follow-up visit #1.
Results of Breathalyzer testing.

These research results will be kept by the researchers only in a research record. The researchers will take steps to make sure that these results are **not** placed in your Emory or Grady Healthcare medical record. The results will **not** be made available to any other healthcare providers who may be giving you treatment. It will be up to you to let your healthcare providers know that you are in a research study.

Other useful study results that are not on this list **will** be placed your Emory or Grady Healthcare medical record. Anyone who has access to your medical record will have access to all results that are placed there. Emory or Grady Healthcare may use these results in caring for you. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA Privacy Rule. On the other hand, some state and federal laws and rules may not protect the research information from disclosure.

Emory or Grady Healthcare does not control results from tests and procedures done at other places. So these results would not be placed in your Emory or Grady Healthcare medical record. They will not likely be available to Emory or Grady Healthcare to help take care of you. Emory or Grady Healthcare also does not have control over any other medical records that you may have with other healthcare providers. Emory or Grady Healthcare will not send any test or procedure results from the study to these providers. So if you decide to be in this study, it is up to you to let them know.

Some tests and procedures that may be done during this study will be reviewed **only** for **research** purposes, **not for your healthcare purposes**. These results will not be reviewed to make decisions about your personal health or treatment. The specific tests or procedures, if any, would be reviewed only for research purposes include:
Neuropsychological testing completed in the ED via DETECT or ANAM.
Neuropsychological testing completed in the GCRC as part of this study protocol on follow-up visit #1.
Results of Breathalyzer testing.

For safety reasons, however, some basic information will be placed in your Emory or Grady Healthcare medical record:

- The fact that you are enrolled in a research study and you gave informed consent to join it
- Contact information for the researcher who is in charge of the study

- A description of health care that would be called for in case of medical problems you may have arising from the study; and
- A description of when and how health care providers may get research information, upon request, that they may need to give you medical care.

We encourage you to let your health care provider know if you decide to take part in this study. That way they can have extra information that can help them to make decisions about your health care.

Costs

There are no costs, research or standard of care related, associated with the study.

There will be no costs to you for participating in this study. You will not be charged for any of the research activities.

Withdrawal from the Study

You have the right to leave a study at any time without penalty. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

The researchers and Department of Defense also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interest;
- You were to object to any future changes that may be made in the study plan;
- or for any other reason.

Questions

Contact Dr. Leon Haley Jr. at 404-616-6419:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research

Contact the Emory Institutional Review Board at 404-712-0720 or 877-503-9797 or irb@emory.edu:

- If you have questions about your rights as a research subject.
- If you have questions, concerns, or complaints about the research.

You may also contact Dr. Curtis Lewis, Senior Vice President for Grady Health System Medical Affairs at (404) 616-4261.

Consent

Please, print your name and sign below if you agree to be in this study. By signing this consent form, you will not give up any of your legal rights. We will give you a copy of the signed consent, to keep.

_____

Name of Subject

_____ _____

Signature of Subject Date Time

_____

Authority of Legally Authorized Representative or Relationship to Subject

_____ _____

Signature of Person Conducting Informed Consent Discussion Date Time

Appendix B

Emory University School of Medicine Research Subject HIPAA Authorization to Use or Disclose Health Information that Identifies You for a Research Study

Study Title: *Electronic Patient Tracking and Electronic Health Record at Grady Health System in Support of Military Training and Research*

Protocol Title: Novel Methods of Neuropsychological Testing in a Level I Trauma Center; *A Comparison of DETECT ANAM, and Standard Neuropsychological Testing*

Study Number:_____

Name of Principal Investigator: Leon L. Haley Jr., MD, MHSA, CPE, FACEP

Subject Name:_____
The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act (HIPAA). We refer to all of these laws in this form as the Privacy Rules. This form explains how we will use your PHI for this study.

Please read this form carefully and if you agree with it, sign it at the end.

Description of Research Study: This is a study of new tools in the assessment of minor traumatic brain injury. In order to evaluate the ability of these tests in measuring your injury, we will need access to your health information.

PHI That Will Be Used/Disclosed:

The PHI that we may use or disclose (share) for this research study includes: the entire medical record, medical history, lab results, and radiology results.

Purposes for Which Your PHI Will Be Used:

If you sign this form, you give us your permission to use your PHI for the conduct and oversight of this research study.

People That Will Use or Disclose Your PHI and Purpose of Use/Disclosure:

Different people and groups will use and disclose your PHI. They will do this only in connection with the research study. The following persons or groups may use and/or disclose your PHI:

The Principal Investigator and the research staff.

The Principal Investigator may use other people and groups to help conduct the study. These people and groups will use your PHI to do this work.

The Department of Defense is the Sponsor of this Research. The Sponsor(s) may use and disclose your PHI to make sure the research is done correctly. They may also use your PHI to collect and analyze the results of the research. The Sponsor may have other people and groups help conduct, oversee, and analyze the study. These people or groups will use your PHI.

The following groups may also use and disclose your PHI. They will do this to make sure the research is done correctly and safely. The groups are:

- the Emory University Institutional Review Board
- the Emory University Office for Clinical Research
- the Emory University Office of Research Compliance
- research monitors and reviewers
- data and safety monitoring boards
- any government agencies who regulate the research including the Office of Human Subjects Research Protections and public health agencies

We will use or disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or elder abuse. We also will comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

Revoking Your Authorization:

You do not have to sign this form. Even if you do, at any time later on you may revoke (take back) your permission. If you want to do this, you must write to:

Dr. Leon L. Haley Jr., MD, MHSA, CPE, FACEP
Principle Investigator
Chief of Emergency Medicine
Associate Professor and Vice-Chair
Department of Emergency Medicine
Emory University School of Medicine
Grady Memorial Hospital Emergency Department
80 Jesse Hill Jr. Dr. SE
Atlanta, GA 30303

After that point, the researchers would not collect any more of your PHI. But they may use or pass along the information you already gave them so they can follow the law, protect your safety, or make sure the research was done properly. If you have any questions about this, please ask.

Other Items You Should Know:

If we disclose information to people who do not have to follow the Privacy Rules, your information will no longer be protected by the Privacy Rules. People who do not have to follow the Privacy Rules can use or disclose your information with others without your permission if

they are allowed to do so by the laws that cover them. Let us know if you have questions about this.

You do not have to sign this form. If you do not sign, you may not participate in the research study or receive research-related testing. You may still receive non-research related treatment.

We will put a copy of your signed informed consent form for the research study and your signed HIPAA Authorization form into any medical record that you may have with Emory Healthcare facilities.

During the study you will generally not have access to records related to the research study. This is to preserve the integrity of the research.

If identifiers are removed from your PHI, then the remaining information will not be subject to the Privacy Rules. It may be used or disclosed with other people or organizations, and/or for other purposes.

Expiration Date: Your permission to use and disclose your PHI will expire. The expiration will be at the end of the research study and any required record-keeping period. **Contacts:** If you have any questions regarding the study, you may call

Dr. Leon L. Haley Jr.
Grady Memorial Hospital Emergency Department
80 Jesse Hill Jr. Dr. SE
Atlanta, GA 30303
404-616-6419

If you have any questions about the study, or your rights as a study subject, you may contact the Emory University Institutional Review Board at 404-712-0720 or 1-877-503-9797, by email at irb@emory.edu. A copy of this form will be given to you.

_____
Signature of Study Subject

Date _____ Time_____

_____
Printed Name of Study Subject OR Subject's Legally Authorized Representative

_____
Signature of Person Obtaining Authorization

_____ _____
Date Time

Study References

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Appendix B
ANAM Device

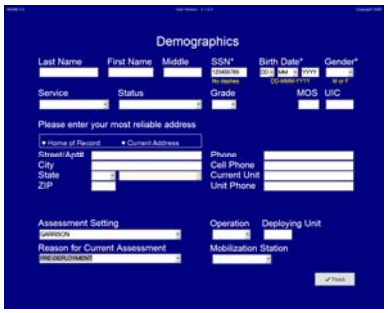
ANAM4™ GMH Test Battery Descriptions

ANAM assesses different basic functions (or domains) of cognition such as attention, reaction time, memory, and concentration. ANAM4 can be self-administered by the user after brief instructions and takes approximately 20-30 minutes to complete.

ANAM4™ GMH Test Battery Descriptions

Descriptions of the individual tests follow in the order of administration.

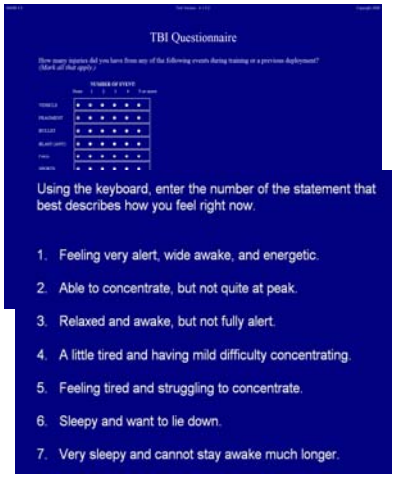
Demographics Module



TEST DESCRIPTION

The demographics module allows users to enter a wide variety of information including name, age, gender, ethnicity, medical diagnosis, medications, and additional comments that the researcher or clinician finds useful.

TBI Questionnaire



TEST DESCRIPTION

The TBI Questionnaire is designed to assess injury history and related symptomology.

Sleep Scale

TEST DESCRIPTION

The user is presented with seven different statements of alertness/sleepiness, ranging from "Feeling very alert, wide awake, and energetic" to "Very sleepy and cannot stay awake much longer." The user is instructed to select the one statement that best matches the current state.

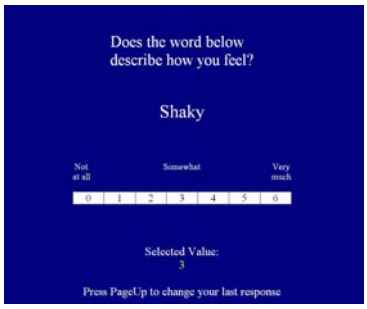
COGNITIVE DOMAIN

The sleepiness scale has been included to identify the examinee's current level of sleepiness or overall arousal level at the time the test is taken.

Mood Scale II - Revised

TEST DESCRIPTION

This test permits self-assessment of the user's mood state in seven categories: Vigor (high energy level), Happiness (positive disposition), Depression (dysphoria), Anger (negative disposition), Fatigue (low energy level), Anxiety (anxiety level), and a new subcategory of Restlessness (motor agitation). The user is presented with a scale of numbered blocks ranging from 0 to 6, with "0" having the verbal anchor “Not at all,” the midpoint "3" labeled “Somewhat” and "6" labeled “Very Much.” The user is presented a series of adjectives, each adjective contributing to one of the mood categories, and is instructed to select the box/number that best represents the current state with respect to the presented adjective.



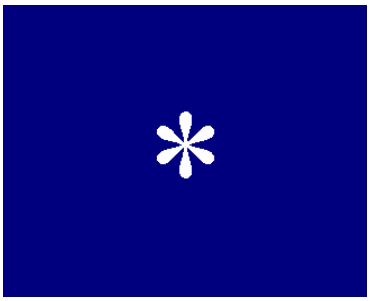
COGNITIVE DOMAIN

The Moodscale2-R is designed to assess either mood state or trait in participants in six subcategories that include Vigor (high energy-level), Happiness (positive disposition), Depression (dysphoria), Anger (negative disposition), Fatigue (low-energy level), and Anxiety (anxiety level).

Simple Reaction Time

TEST DESCRIPTION

This test measures simple reaction time by presenting the user with a series of "*" symbols on the display. The user is instructed to respond as quickly as possible by pressing a button each time the stimulus appears.



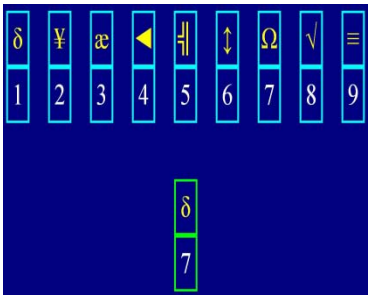
COGNITIVE DOMAIN

This task measures visuomotor processing speed, simple motor speed, and attention.

Code Substitution - Learning

TEST DESCRIPTION

In this test the user must compare a displayed digit-symbol pair with a set of defined digit-symbol pairs, or the *key*. The user presses designated buttons to indicate whether the pair in question is correct or incorrect relative to the key. In the Learning phase (simultaneous presentation mode), the defined pairs are presented on the screen along with the digit-symbol pair in question.



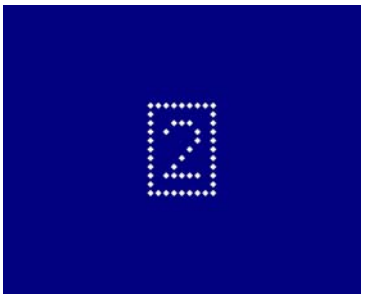
COGNITIVE DOMAIN

This test measures visual scanning, visual perception, attention, associative learning, and information processing speed.

Procedural Reaction Time

TEST DESCRIPTION

There are three possible blocks of trials for this test. In the Basic Block, the user is presented with a number presented on the display using a large dot matrix (either a 2, 3, 4, or 5). The user is instructed to press one designated button for a "low" number (2 or 3) and another designated button for a "high" number (4 or 5).



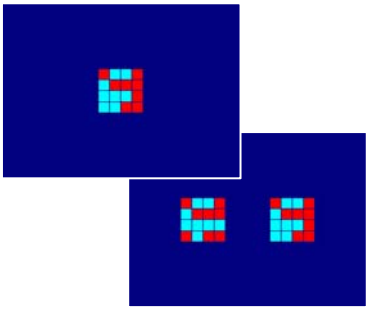
COGNITIVE DOMAIN

This test measures the information processing speed, visuomotor reaction time, and attention.

Matching to Sample

TEST DESCRIPTION

During this test the user views a pattern produced by eight shaded cells in a 4x4 sample grid. The sample is then removed and two comparison patterns are displayed side by side. One grid is identical to the sample grid and the other grid differs by one shaded cell. The user is instructed to press a designated button to select the grid that matches the sample.



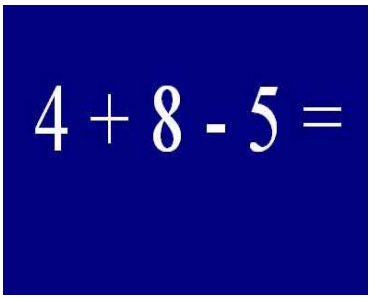
COGNITIVE DOMAIN

This test is intended as a measure of visual-spatial processing, working memory, and visual recognition memory.

Mathematical Processing

TEST DESCRIPTION

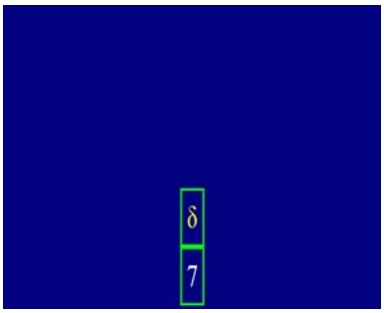
During this task, an arithmetic problem involving three single-digit numbers and two operators is displayed (e.g., "5 - 2 + 3 ="). The user presses buttons to indicate whether the answer to the problem is less than five or greater than five.



COGNITIVE DOMAIN

Results of this test are used as an index of basic computational skills, concentration, and working memory

Code Substitution – Delayed (Recognition)



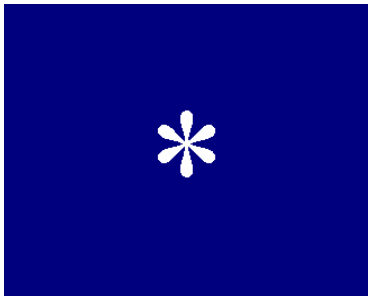
TEST DESCRIPTION

In this test the user is presented with a digit-symbol pair and must decide from memory if this pairing is correct based on the key presented during the Code Substitution – Learning test taken earlier in the test battery. The user presses designated buttons to indicate whether the pair in question represents a correct or incorrect match based on the earlier presented key.

COGNITIVE DOMAIN

This test provides a measure of learning and delayed visual recognition memory.

Simple Reaction Time



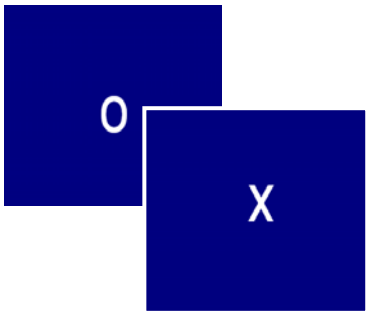
TEST DESCRIPTION

This is a repeat of the Simple Reaction Time test presented earlier in the battery. This test measures simple reaction time by presenting the user with a series of "*" symbols on the display. The user is instructed to respond as quickly as possible by pressing a button each time the stimulus appears.

COGNITIVE DOMAIN

Results of this test are used as an index of attention (i.e., reaction time & vigilance) and visuo-motor response timing.

Go/No-Go



TEST DESCRIPTION

The user is presented with two characters, “x” and “o”. The user is instructed to respond as quickly as possible to the “x” by pressing a button each time the stimulus appears. When the “o” appears, the user is to do nothing (inhibit response).

COGNITIVE DOMAIN

This test assesses response inhibition.

SYMPTOMS CHECKLIST

TEST DESCRIPTION

The user is presented with 21 symptoms. The user is to rate each symptom on a scale from 0 (Not Present) to 6 (Severe).

COGNITIVE DOMAIN

The Symptoms Checklist is designed to monitor the frequency and severity of subjective symptoms.

Appendix C
DETECT Guides

DETECT Interpretation Guide for Physicians

Background
Information specific to medical personnel beyond what is in the patient document such as what further diagnostic tests a neurologist will perform

Important Points
- Cognition is unique to the individual
- Know your patient
- Understand prior impairment
    - Existing disease
    - Birth Defects
    - Previous brain trauma
- Many things can affect cognitive score
    - Immediate/temporary score impacts
        - Drugs and Alcohol
        - Prescription Drug Interactions
        - Tiredness
        - Stress
        - Pregnancy (?)
    - Long Term score impacts
        - MCI
        - Dementia
        - Alzheimer's Disease
        - Vascular Dementia
        - Pick's Disease
        - Depression related Dementia
        - HIV/AIDS related Dementia
        - Parkinson's related Dementia

Interpretation of the ZScore
- As a standalone score
    - Normal
        - Retest as appropriate per the table

	50-60	61-70	71-80	81-90	Over 90
Family History	yearly	yearly	3 x year	3x year	2x year
No Family History	every 3 years	yearly	2 x year	2x year	2x year

        - Council patient on Cognitive Wellness Lifestyle
    - Possible Impairment (MCI)
        - May be 'Normal' for the patient
            - Check their history
        - May be a point in time aberration
            - Check for drug interactions (changes or new prescriptions)
            - Retest in 6-12 weeks
            - If decline is still existent and still minor
                - Council patient on Cognitive Wellness Lifestyle
            - Have the patient or family member contact immediately if further decline noted
    - Definite Impairment (Dementia)

        - Known disease or condition
            - Is this a retest to monitor progression or therapy?
            - New result
                - Refer for further testing and identification of the problem
        - Is this a continuation of prior probable deterioration?
                - Discuss option with patient and family
                - Refer for further testing and identification of the problem
        - Is this a sudden and rapid decline?
                - Immediately refer for further testing and identification of the problem

Medical Technician Instructions

- Patient Usage
    - Cleaning
        - Lightly wipe down all surfaces of the device with an alcohol wipe immediately prior to a patient's usage
    - Power On
        - Push power on button
    - Battery Check
        - Make sure at least 2? LEDs are lit to ensure enough battery life for the test
    - Data Entry
        - Enter personal ID for the person assisting the Patient and verify
        - Enter Patient ID and verify
        - Select test as designated by the physician
        - Select appropriate language for the patient
    - Patient Placement
        - Assist patient with placement of the visor in a comfortable position
        - Hand patient the controller making sure left button is on the patients left side
    - Verify Patient can see and hear
        - Instructions will tell the patient to ask for assistance if thy cannot see or hear the test clearly
    - Interim Check
        - Ensure patient is continuing test
        - Check that Progress indicators are consistent with time passed for the test
    - Test Complete
        - Remove Device
        - Note raw ZScore
            - Annotate the patients medical record with the ZScore off the LCD panel for physician review
- Upload
    - Make sure power supply is plugged in and green LED is on
    - Plug power supply barrel connector into power supply port on the device
    - Make sure the Ethernet cable is connected to the appropriate office network plug
    - Plug the Ethernet cable into the Internet port on the device
    - Make sure the LEDs blink 3 times indicating network connection
        - If not contact your network administrator
- Access Patient ZScore report
    - Log into the Zenda Lifetime Electronic Cognitive Health Record web site
    - Select 'Test Results' from the menu bar
    - Enter the date range for ZScore test results you require
    - Click 'Apply' to retrieve tests for those dates
    - Click 'ZScore' for a patient and their ZScore report is presented and can be
        - Printed
        - Downloaded in PDF format (requires Acrobat Reader)

        - Downloaded in Excel format (requires Excel)
- Load Patient Data
    - Automated
        - Follow the instructions for your electronic medical records system and create a CSV file in this format
            - MRN
            - Etc.
    - Manual
    - Log into the Zenda Lifetime Electronic Cognitive Health Record web site
        - Select ‘Patients’ from the Menu Bar
        - On the Patients List Screen Select ‘Add Patient’
        - On the patient entry screen enter Social Security number
            - If found the patient information will be filled in – please ensure this is indeed the correct patient and that the SS number was not mis-entered.
            - If not found enter all available data in the health record
                - At a minimum the required fields as marked with a red asterisk must be entered.

Appendix E
Goal Directed Therapy for Traumatic Brain Injury – a retrospective analysis

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I. Abstract

The purpose of this study is to determine the current compliance with widely accepted guidelines for the management of severe traumatic brain injury (TBI) patients and assess the overall mortality of this cohort at Grady Memorial Hospital (GMH). Objectives of this study include: a) Develop a data extraction tool for monitoring compliance with Goal Directed Therapy (GDT) guidelines for the management of acute TBI in the Emergency Department and b) assess past compliance with evidence-based management of TBI. The study population includes patients with blunt-mechanism trauma with a Glasgow Coma Scale (GCS) of 3 – 12. The data extraction tool will be used for retrospective chart review of all GMH patients meeting criteria over the previous two year span.

II. Introduction and Background

Every 15 seconds, a U.S. citizen sustains a traumatic brain injury (TBI), amounting to a yearly TBI incidence of 1.5 – 2 million. The annual morbidity, mortality, and cost associated with TBI are significant: 50,000 deaths, 80,000 disabled, 235,000 hospitalizations, and $60 billion in aggregate annual cost.[1,2] TBI is also important to the U.S. military. An estimated 10-to-20 percent of returning Iraq and Afghanistan veterans have suffered combat-related TBI to date.3 This may be a conservative figure due to lack of in-the-field screening. To this extent, the Department of Defense (DoD) has taken a vested interest in the evaluation and management of TBI and has provided the funding – – for the larger study that includes this project.

Although compelling data suggests there are several modifiable clinical factors that worsen outcomes – including hypotension and hypoxemia[4] – there is presently an enormous amount of variability in the management of TBI patients. This variability in care extends from the pre-hospital (EMS) and emergency department phase all the way to the ICU phase.[5] Despite the development of consensus guidelines for management of complications of TBI (ie increased intracranial pressure), numerous TBI interventional clinical trials have failed – due in part to persistent variability in care.

Goal-Directed-Therapy (GDT) is a technique that incorporates evidence based guidelines into an aggressive management strategy based on meeting target physiological parameters. It has been shown to improve outcomes in the treatment of sepsis and post cardiac surgery care, in addition to other medical conditions.[6]

Hypothesis

There is a lack of compliance with current guidelines for the management of acute TBI as evidenced by a high degree of variability in the implementation of interventions for maintaining a set of physiological parameters.
There will be a lower in-hospital mortality rate in the subgroup of patients who were managed more closely to the guidelines.

Primary and Secondary Aims

Primary Aim 1: Assess compliance with evidence-based management for TBI and current variability of TBI treatment in the GMH Emergency Care Center (ECC) in the previous two year span.

Secondary Aim 1: Ascertain baseline 30-day mortality among moderate and severe TBI patients admitted to GMH

Secondary Aim 2: Compare the in-hospital mortality of acute TBI patients treated in compliance with the TBI guidelines vs. patients not managed in accordance with the TBI guidelines.

IV. Research Design

Setting: Grady Memorial Hospital (GMH) Emergency Care Center (ECC)
Study Design: Create an audit tool for retrospective chart review of pre-GDT implementation TBI patients over a two year span to assess: a) outcome measures (see below) and b) management methods , using GMH TRACS registry system (Trauma Registry system)

Study Subjects: Adults with the following inclusion criteria:

Inclusion Criteria	**Rationale**
Blunt-mechanism trauma	Anatomic/physiologic differences from penetrating trauma
Severe Brain Injury (iGCS 3 – 12)	Group most likely to show benefit in primary outcome

Randomization: No randomization, consecutive patients admitted to the Grady ECC with an arrival GCS of 3-12 will be included in the data analysis.
Outcome Measures: 1. Proportion of physiological parameters met in the acute management phase (ECC), 2. Proportion of patients in whom the TBI management guidelines were followed,

3. Inpatient mortality
Analyses: Descriptive statistics will be used to describe guidelines compliance as a whole, within subject and between subjects. Proportional odds will be used to compare groups with respect to compliance and outcomes. Contingency table analysis will be used to compare rates of mortality between individual physiological parameters. Cox proportional hazards will be used to compare

survival curves after adjusting for other important covariates such as age, gender, injury severity, pupil response, and CT findings.

Relevance and future Goals: The data from this pilot study will inform us of the current compliance rate of a set of widely adopted management guidelines and the effect on mortality. Data from this study will be used to develop a protocol for educational interventions and further study as to whether tightly controlled GDT in the early stages after an acute TBI can improve outcome. This is of keen interest to both civilian trauma centers and the military. Future prospective studies would confirm these findings and provide further support for, and increased justification for the broad implementation of GDT for acute TBI. The impact could be better patient outcomes and decreased treatment variability in trauma centers in the US.

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